

**Piotr Wysocki**

Zachodniopomorskie Centrum Onkologii, Szczecin

# Palliative systemic treatment of bladder cancer

**Address for correspondence:**

Prof. dr hab. n. med. Piotr Wysocki  
Zachodniopomorskie Centrum Onkologii  
Szczecin

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**ABSTRACT**

The systemic treatment of the bladder cancer is challenging. It is so due to moderate efficacy of chemotherapy and because of the restrictions secondary to the patient's general performance status as well as an inadequate organ function (mainly renal function). The standards of the first line systemic treatment are established. The chemotherapy regimens containing platine derivatives (preferably cisplatin) such as PG or MVAC are administered routinely. However such standard regarding the second line of systemic treatment is not defined. This reflects the lack of reliable scientific evidence supporting the chemotherapy use at this stage of the disease. Among several drugs being considered as the second line chemotherapy it is only vinflunine that proved its activity in phase III clinical trial and compared to the best supportive care improves prognosis and positively influence the quality of life.

**Key words:** bladder cancer, chemotherapy, palliative treatment

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**Epidemiology**

The bladder cancer, as the second most frequent genitourinary cancer, is mainly recognised in elderly people (at age between 60 and 70 years), and the average age at diagnosis is 70 years. It is about 3–4 times more frequent in men than in women. In 2011 there were 4700 new cases in Poland diagnosed in men and 1300 in women. In 2012, 2400 men and 650 women died of bladder cancer in Poland [1].

The infiltration of the muscle layer of the bladder is recognised in about 25% of cases of bladder cancer. Over 90% of all bladder cancers are developed from the urothelium (carcinoma urotheliale).

The five-year survival in patients with bladder cancer in Europe is 68% (in Poland — about 62%) [1], while only 15% of patients with metastatic disease survive for five years.

**Adjuvant chemotherapy**

Patients with locally advanced bladder cancer and cT2–4a cN0M0 tumours, who are in good performance

status (ECOG  $\leq 1$ ), should undergo preoperative cisplatin-based chemotherapy as it increases the rate of five-year survival by 5–8%. In patients who have undergone primary radical surgery (cystectomy) and are diagnosed with  $\geq T3$  tumours or with regional lymph node involvement, adjuvant chemotherapy with cisplatin may be considered [2].

**Palliative chemotherapy**

Despite the aggressive radical treatment about half of the cystectomised patients have recurrent disease. In the majority of cases it is a distant recurrence, and only in about 10–30% of patients is local recurrence diagnosed. In patients with distant metastatic lesions or unresectable local recurrence systemic treatment with chemotherapy should be considered. The prognosis of patients who undergo the chemotherapy depends on the presence of unfavourable prognostic factors such as low performance status (Karnofsky score  $< 80\%$ ) and distant metastases [3]. The choice of the chemotherapy regimen depends on several factors (i.e. comorbidities and general performance status). Cisplatin, as the drug

of choice with proved activity in the first line treatment of the bladder cancer, has substantial toxicity (nephrotoxicity, neurotoxicity, and myelotoxicity). For this reason, and taking into consideration the typical profile of patient with bladder cancer (elderly, usually with coexisting impaired renal function, circulatory insufficiency related to — for example — long-term nicotine addiction), less active regimens with carboplatin or without platinum derivatives are administered. In the case of patients in pure performance status with the presence of distant metastatic spread the efficacy of the systemic treatment is minimal and its tolerance is usually bad. The standard of care in such cases is best supportive care only.

### First-line chemotherapy

The combination regimens of cisplatin and gemcitabine (GC regimen) or methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC regimen) are most frequently used as the first line of palliative chemotherapy for bladder cancer. The GC regimen is usually used as the chemotherapy of choice in the first-line palliative treatment of advanced/metastatic bladder cancer due to its relatively favourable toxicity profile when compared to a classic M-VAC regimen while preserving the clinical efficacy with no differences between the two regimens [in terms of overall survival (OS); progression-free survival (PFS)] [4]. However, it has been proven that modification of classic M-VAC regimen, called HD-MVAC regimen, being administered every 14 days with the support of granulopoietins is significantly more effective (objective response rate — 72% vs. 58%; OS — decrease in relative risk of death by 24%; PFS — decrease in relative risk of progression by 27%) than classic M-VAC and significantly less toxic [3]. Although the direct comparison of HD-MVAC and GC regimens is not available the first seems to be the treatment of choice in patients in good performance status and with high tumour burden.

In patients with impaired renal function carboplatin is used instead of cisplatin; however, it must be emphasised that equal efficacy of the two drugs has not been proven [6]. Some patients who cannot be treated with platinum derivatives may benefit from gemcitabine monotherapy or a combination of paclitaxel and gemcitabine.

### Second-line chemotherapy

The relevance of use as well as the inclusion criteria and the administration of second-line chemotherapy for bladder cancer are controversial. Taking into account the patient's performance status, restricted organ function, long-term adverse events, and toxicity of the

first-line chemotherapy as well as the relatively low chemo-sensitivity of bladder cancer cells, the use of second-line systemic treatment seems to be unreasonable in the majority of patients, and in such cases the introduction of complex best supportive care is the treatment of choice. However, in some patients the good performance status allows consideration of use of systemic treatment of the second line. Due to restricted clinical data with high level of creditability the recommended standard of care in patients who have failed to benefit from the first line of the systemic treatment does not exist. In its 2015 guidelines the National Comprehensive Cancer Network (NCCN) recommend referral of patients to clinical trials with use of novel drugs or therapeutic strategies [7]. According to international recommendations (i.e. NCCN or European Association of Urology — EAU) monotherapy with several cytotoxic drugs may be considered (taxanes/taxoids, gemcitabine, cisplatin, carboplatin, doxorubicin, ifosfamide, methotrexate, pemetrexed, or vinblastine) [7, 8]. There are no data to support the positive impact of the drugs mentioned above on the prognosis of patients undergoing second-line chemotherapy. The available data — from phase II clinical trials on small populations of patients with bladder cancer (usually < 40 patients) — indicate a small objective response rate (usually less than 20%) (Table 1). Vinflunine (VFL), as the representative of novel generation microtubule polymerisation inhibitors, is the only drug approved for second-line chemotherapy of patients with advanced bladder cancer. The drug has higher in vitro anti-cancer activity when compared to classic *vinca alkaloids* and has lower affinity to microtubules than *vinca alkaloids*, which allows a lower neurotoxic effect of VFL [9]. In a phase III trial in a population of 370 patients with advanced bladder cancer and with failure of first-line cisplatin-containing chemotherapy, vinflunine with best supportive care (BSC) was compared to BSC alone [10, 11]. The primary end-point was the difference in OS. After 45 months of follow-up — in per-protocol-population (about 5% of patients enrolled to the trial had an unproven disease progression on the first line chemotherapy) — a significant improvement of OS was shown in the study drug group. Median OS was 6.9 months versus 4.3 months, respectively, in the VFL + BSC and BSC arm (the relative risk of death decreased by 22%) [11]. The objective responses were observed only in patients in the VFL + BSC arm (8.6%) [10]. The stable disease was observed in 46.5% of patients (VFL + BSC) and 27.1% of patients (BSC). The difference in PFS medians (3.0 months versus 1.5 months) favouring VFL was statistically significant.

The use of active systemic treatment in patients with advanced bladder cancer after first-line chemotherapy failure is related to adverse events that are usually more intensive when compared to their intensity observed

**Table 1. Activity of drugs used as monotherapy in second-line palliative treatment in patients with bladder cancer (phase II clinical trials)**

Drug	Number of patients	Responses (%)	Progression-free survival (months)
Paclitaxel every 7 days	31	10	2.2
Irinotecan	40	5	2.1
Ifosfamide	56	20	2.4
Gemcitabine	30	11	4.9
Vinflunine	51	18	3.0
Gefitinib	31	3	–
Sorafenib	27	0	–
Sunitinib	45	7	2.4
Lapatinib	59	3	2

during previous therapy. The common grade 3/4 adverse events related to VFL and observed in > 4% of patients were: neutropaenia (50% of patients), anaemia (19%), constipation (16%), and thrombocytopaenia (6%). The quality-of-life analysis, as one of the crucial elements of the trial and based on detailed assessment with European Organisation for Research and Treatment of Cancer — Quality of Life Questionnaires (EORTC QLQ) C30, revealed that VFL does not negatively influence the quality of life as compared to supportive care. Despite the continuous and gradual decrease of quality of life observed in the control arm, in the study drug group (VFL + BSC) the quality of life parameters improved after 18 weeks of treatment [10]. The active treatment decreased the proportion of patients requiring palliative radiotherapy (4% vs. 24%) and delayed the need for the introduction of other palliative procedures (5% vs. 26% during six months of follow-up).

In 2015 the therapeutic procedures currently used in Poland in patients with advanced bladder cancer after first-line chemotherapy failure were reviewed. The analysis based on the data from 12 reference cancer centres in Poland revealed that about half of the patients receive second-line chemotherapy and the rest of this population receive supportive care only (i.e. analgesics, anticoagulants/prophylaxis of thromboembolic events, as well as antibiotics or blood products). Surprisingly, despite well-defined international guidelines, chemotherapy was mainly based on combined regimens consisting of two drugs (gemcitabine + cisplatin or gemcitabine + paclitaxel) and more seldom on monotherapy with paclitaxel or gemcitabine.

## Summary

The decision regarding the choice of second-line palliative treatment in patients with advanced bladder

cancer should always take into account the patient's general performance status, assessment of organ function (especially kidneys), the efficacy and toxicity of previous systemic therapy, and the achieved time to disease progression. In patients with very good performance status and adequate renal function, who tolerated the first-line cisplatin-based treatment well and achieved long-lasting responses (longer than six months), re-challenge with previously used drugs may be considered [12]. However, such population is rarely observed in clinical practice, and in the majority of patients contraindications for platinum-derivatives used are present (poor performance status, impaired renal function, audiometric deficits, signs of grade  $\geq 2$  peripheral neuropathy, or grade 3 cardiac insufficiency according to New York Heart Association (NYHA) classification) [6, 11]. For these reasons the use of drugs other than platinum-derivative cytotoxic medications for the second-line treatment should be considered in daily clinical practice. Among them only VFL has highly credible data available that supports the activity of this mitotic spindle inhibitor in palliative systemic treatment — favourable impact on prognosis (OS) and quality of life in patients with advanced bladder cancer after failure of the first line palliative chemotherapy.

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